MANAGEMENT EPIDEMICS USING HIGH COMPLEXITY MATHEMATICAL MODELING

PART V: SEIMR/R-S General Epidemic Model. Theory, Validation and Application in Mexican Regions

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ABSTRACT

SEIMR/R-S corresponds to a generalized mathematical model of pandemics that enhances traditional, aggregated simulation models when considering inter-regional impacts in a macro region (conurbed); SEIMR/R-S also considers the impact of modeling the population divided into socio-demographic segments based on age and economic stratum (it is possible to include other dimensions, for example: ethnics, sex, …).

SEIMR/R-S is the core of the SEIMR/R-S/OPT epidemic management optimization model that determines optimal policies (mitigation and confinement) considering the spatial distribution of the population, segmented socio-demographically. The formulation of SEIMR/R-S/OPT is presented in another "paper" describing its implementation in GAMS and AMPL, and the implementation for the case of Bogota.

SEIMR/R-S can be understood and used by any epidemiologist, and/or physician, working with SIR, SEIR or similar simulation models, and by professionals working on the issue of public policies for epidemic control.

1. EPIDEMIC & CONTROL POLICIES MODEL

The **SEIMR/R-S** is a detailed epidemic model that is the result of integrating the **SIR**, **SEIR** and **SEI3RD** model; in these standard models the population is grouped in only one homogenous group. **SEIMR/R-S** extends the modeling to a multi-segment-sociodemographic multi-region system.

SEIMR/R-S model describes the epidemic with following states:

S **Susceptible:** initially covers all population that potentially can be infected (SU)

E **Exposed:** Population that has been infected and are in an incubation (latency) period (EX). The model SIR does not include this state.

IM **Multi-Infected:** Population that has been infected and has active the pathogen in different states of development (I0, I1,I2, … , IN). The active infected states are ordered according to the severity of the infection. The modeled SIR and SEIR consider only one infected state. For convenience, the last state is called "IN"

R **Recovered:** Recovering population (RE)

R-S is related with the Region-Segment model that considers multiples regions where live people classified in multiples socio-demographics segments.

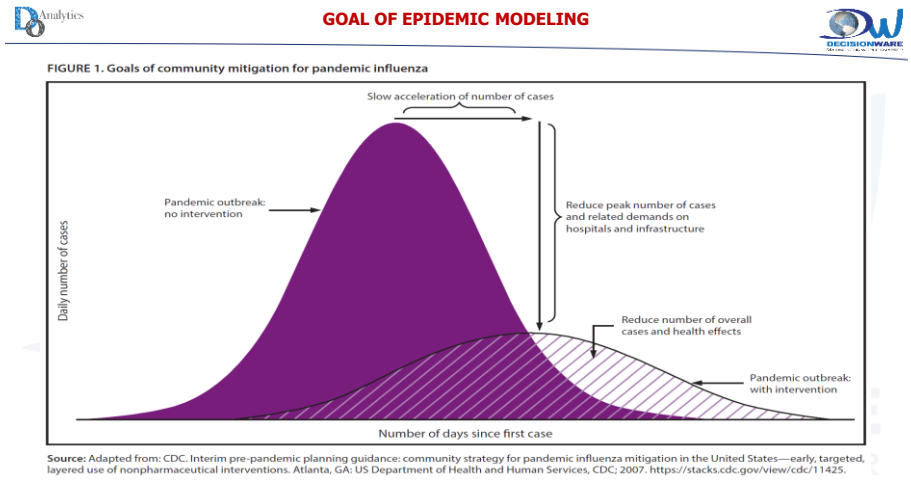
1.1. CONCEPTUAL FRAMEWORK

The following documents have been referenced and used for writing the following numerals:

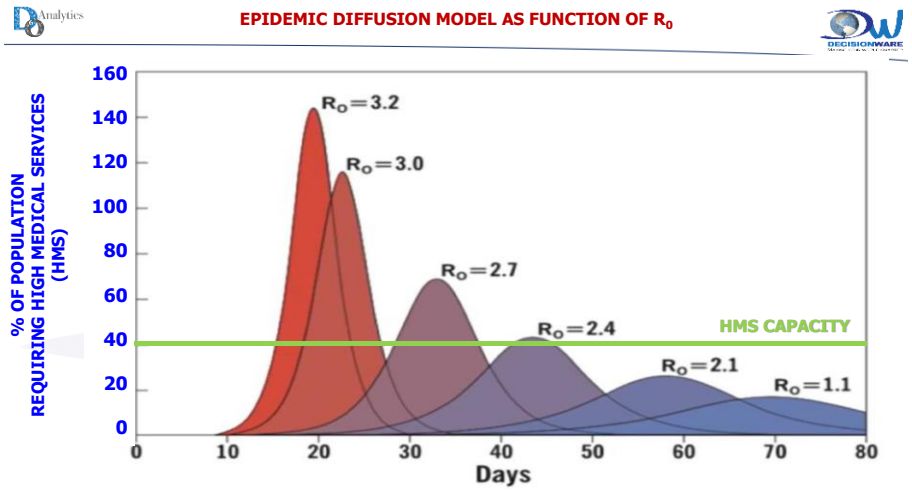
- Brauer, F. and Castillo-Chavez, C. (2000). Mathematical Models in Population Biology and Epidemiology. Springer, New York, 2000.
- Cai, Y., Kang, Y., Banerjee, M., & Wang, W. (2015). A stochastic SIRS epidemic model with infectious force under intervention strategies. Journal of Differential Equations, 259(12), 7463-7502.
- Carcione, J., Santos J. E., Bagaini, C. and Jing, Ba. (2020) A Simulation of a COVID-19 Epidemic Based on a Deterministic SEIR Model.
- Erdem, M., Safan, M., & Castillo-Chavez, C. (2017). Mathematical analysis of an SIQR influenza model with imperfect quarantine. Bulletin of mathematical biology, 79(7), 1612-1636.
- Eubank, S., Eckstrand, I., Lewis, B., Venkatramanan, S., Marathe, M., & Barrett, C. L. (2020). Commentary on Ferguson, et al.,"Impact of Non-pharmaceutical Interventions (NPIs) to Reduce COVID-19 Mortality and Healthcare Demand". Bulletin of Mathematical Biology, 82, 1-7.

- Ferguson, N., Laydon, D., Nedjati Gilani, G., Imai, N., Ainslie, K., Baguelin, M., ... & Dighe, A. (2020). Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand.
- Hethcote, H. W. (2000). "The Mathematics of Infectious Diseases." SIAM Review 42.4 (2000), pp. 599–653.
- Huang G. (2016). Artificial infectious disease optimization: A SEIQR epidemic dynamic model-based function optimization algorithm. Swarm and evolutionary computation, 27, 31–67. https://doi.org/10.1016/j.swevo.2015.09.007
- Jing, W., Jin, Z., & Zhang, J. (2018). An SIR pairwise epidemic model with infection age and demography. Journal of biological dynamics, 12(1), 486-508.
- Kermack, W.O. and Mc Kendrick, A. G.,(1927) "Contributions to the Mathematical Theory of Epidemics, Part I". Proc. R. Soc. London, Ser. A, 115, 1927, 700-721.
- Liu M. and Liang, J. (2013). Dynamic optimization model for allocating medical resources in epidemic controlling. Journal of Industrial Engineering and Management JIEM, 2013 – 6(1):73-88 – Online ISSN: 2013-0953
- Massad, E., Bruattini, N.M., Coutinho, B. A. F. and Lopez, F. L., (2007). "The 1918 Influenza An Epidemic in the City" of Sao Paulo", Brazil, Medical Hypotheses, 68, 2007, 442-445
- Mejía Becerra, J. D. et. al. (2020). "Modelación Matemática de la Propagación del SARS-CoV-2 en la Ciudad de Bogotá. Documento de Circulación Informal
- Pang, W. (2020). Public Health Policy: COVID-19 Epidemic and SEIR Model with Asymptomatic Viral Carriers. Department of Mathematics and Statistics, McMaster University arXiv:2004.06311v1 [q-bio.PE] 14 Apr 2020.
- Radulescu, A., & Cavanagh, K. (2020). Management strategies in a SEIR model of COVID 19 community spread. arXiv preprint arXiv:2003.11150.
- Samsuzzoha, Md. (2012) . "A Study on Numerical Solutions of Epidemic Models". Doctoral Thesis, Swinburne University of Technology, Australia, 2012.

The goal of epidemic control strategies is to reduce R_0. This can be achieved by reducing susceptibility or contact rates in the population or the infectiousness of infected populations. The potential effectiveness of medical intervention by varying the infectiousness of infected populations and nonmedical interventions by reducing the contact rates in the population have been examined. In medical intervention, use of vaccines and/or antiviral agents for case of treatment can increase the recovery rate and reduce the death rate. On the other hand, in nonmedical interventions, reducing population contact rates through social distancing and travel restrictions can reduce the impact on the transmission process.



Control of an outbreak relies partly on identification of the disease parameters that lead to a significant reduction of the basic reproduction number $\mathbf{R_0}$ that may be function of several parameters of which γ, the recovery rate for clinically ill and β, the transmission coefficient, are the most sensitive parameters. These two parameters can be controlled by medical intervention and nonmedical interventions.



The modeling of epidemics in a solidly developed area of scientific knowledge, widely studied based on simulation models. The master table of epidemic models shows some of the best-known models

TABLE: MAE_EMO			
STATE (COD_EMO)	**DESCRIPTION (DIN_EMO)**	**Reference (COM_EMO)**	**Imple mented**
SIR	Susceptibility (S), Infection (I) and Recovery (R)	Kermack & Mc Kendrick (1927) Jing (2018)	YES
SEIR	Susceptibility (S), Exposure (E), Infection (I) and Recovery (R)	Hethcote (2000)	YES
SEIRA	Susceptibility (S), Exposure (E), Infection (I) and Recovery (R)		NOT
SEI3RD	Susceptibility (S), Exposure (E), 3+1 Infection States (I3), Recovery (R) and Death (D)	Mejía Becerra et. al. (2020)	YES
SEIQR	Susceptibility (S), Exposure (E), Infection (I), Quarantine (Q) and Recovery (R)	Huang (2016)	NOT
SIRS	Susceptibility (S), Infection (I), Recovery (R) and Susceptibility (S)	Cai (2015)	NOT
…	…	…	NOT
SEIMR/R-S			YES

This Part presents the mathematical formulation of the SIR and SEIR models. The SEI3RD is presented in the **Part IV: Epidemic Optimization Model Applied to Bogota City**.

Then, an epidemiological model is defined based on differential equations that explain the evolution of the process without human intervention. These differential equations can be established based on the population (number of people) who are in a certain "epidemic" state or based on the fraction of the population that is in that state. The epidemic models are nonlinear systems of ordinary differential equations, traditionally this equations system is solved using simulation models based in a discrete approximation for continuous derivatives, be it over time or space. There are many possible schemes. These models are used to analyze several widely discussed (predefined) scenarios and provide evidence on their effectiveness and are not oriented to get the optimal solution of a mix of control policies.

The added value by mathematical programming approach is to convert simulation models into optimization models to be able to combine them with other mathematical programming models, following the principles of structured mathematical modeling that allows join multiple problems of mathematical programming in a single model. Based on the above, the formulation of the models is done by means of algebraic equations that represent how the epidemiological process evolves during the planning horizon.

For the optimization epidemic modeling, the approach is based on multiple state chains that can be associated with semi-Markov chains; initially, it was proposed to model based on the approach of semi-Markovian processes (changing transition matrices over time) but such an approach brings multiple complications in the math formulation of probabilities.

After analyzing the implementation of main (most known) epidemiological models (SIR, SEIR), it was decided to directly model discrete versions of differential equations as they maintain direct connection with biological parameters, which facilitates the connection of these parameters with socio-demographic segments.

Therefore, all epidemiological models considered should be formulated in one of the following terms.

- The time unit of the differential equations is one day.
- The states contain the fraction of the population in each state.
- The time of the optimization model may be divided in periods of multiple days (one week, seven days). In this case, the integration of the differential equations must be made using calculated parameters.

The epidemic states are showed in the master table **MAE_STA** that describes the states. The models will be implemented using this nomenclature. The table includes the symbol used in the original models and the code using in the information system to reference the state.

EPIDEMIC STATES - TABLE: MAE_STA			
MODEL SYMBOL	**EPIDEMIC STATE (COD_STA)**	**DESCRIPTION (DIN_STA)**	**COMMENTS (DLIN_STA)**
S	SU	Susceptible Population	Those individuals who have not been exposed to the pathogen and are susceptible to being infected by it.
E	EX	Exposed Population	Those individuals who are in the latency state; that is, they have been inoculated by the pathogen but are not yet infectious
I	IN	Infected Population	In SIR and SEIR models is infected population. It must be the most critical state for infected people; this is important for models that have more than one epidemic states to describe the infection process.
	IU	Infected Population Unattended	Individuals that require hospital attention and do not received hospital ty attention
	ED	Epidemic Dead	Individuals who fail the infection and die.
	CD	Collateral Dead	Individuals who die by during the epidemic by reasons different to the epidemic. Minimize this population is the goal of the optimization when the epidemic in management isolated, ignoring the economic impact.
	ND	Natural Dead	Individuals who die by other reason different to the epidemic
	NP	New Population	
R	RE	Recovered Population	Those individuals recover from infection, having developed antibodies. In most of the models they cannot be re-infected.

EPIDEMIC STATES - TABLE: MAE_STA			
MODEL SYMBOL	**EPIDEMIC STATE (COD_STA)**	**DESCRIPTION (DIN_STA)**	**COMMENTS (DLIN_STA)**
STANDARD STATES MBC-SEI3RD MODEL			
	ED	Epidemic Dead	Individuals who fail the infection and die.
E	EX	Exposed Population	Those individuals who are in the latency state; that is, they have been inoculated by the pathogen but are not yet infectious
I_0	I0	Asymptomatic Infectious	Those individuals in the population who have been inoculated by the virus are infectious but have not developed symptoms. Those infected in this state rarely learn that they have been infected.
I_1	I1	Moderate Symptoms Infectious	Those individuals in the population who are infectious and have mild or moderate symptoms. They are those who can be given management of the disease at home.
I_2	I2	Severe Symptoms Infectious	Those individuals in the population who are infectious and have severe but not critical symptoms. Individuals present in this state require hospitalization.
I_3	IN	Critical Symptoms Infectious	It must be the most critical state for infected people; this is important for models that have more than one epidemic states to describe the infection process. In SIR and SEIR models is infected population
	ND	Natural Dead	Individuals who die by other reason different to the epidemic
	NP	New Population	
R	RE	Recovered Population	Those individuals recover from infection, having developed antibodies. In most of the models they cannot be re-infected.
S	SU	Susceptible Population	Those individuals who have not been exposed to the pathogen and are susceptible to being infected by it.

EPIDEMIC STATES - TABLE: MAE_STA			
MODEL SYMBOL	**EPIDEMIC STATE (COD_STA)**	**DESCRIPTION (DIN_STA)**	**COMMENTS (DLIN_STA)**
ADDITIONAL CAPACITY STATES MBC-SEI3RD MODEL			
	IU_2 IU_3	Infected Population Unattended	Individuals that require hospital attention and do not received hospital ty attention in state I_2, I_3, …
	CD	Collateral Dead	Individuals who die by during the epidemic by reasons different to the epidemic.

The measurements used must be equal for all models

Measurement Unit Master Table: MAE_UND	
Measurement Unit COD_UND	**Description DES_UND**
1/peo-day	1/ persons-day
fpo/day	Fraction of population per day
peo-day	Persons-day

One of the main limitations of the traditional approach is to assume that the entire population is homogeneous with respect to its epidemiological behavior. It is well known that the epidemic manifests differently in each socio-demographic stratum and that the composition of socio-demographic segments depends on each region.

In order to enhance the model to be useful in real cases, it is assumed that there is a different pandemic (because it has different parameters) for each pair <region, demographic-segment These hypotheses may vary according to each case study. In this case, reference has been made to the data used to control the epidemic used in Bogotá. It should be noted that the parameters of each epidemiological model vary in quantity but cannot vary in the form of calculation, since they are parameters as the same case, which is studied with different mathematical models.

The models are studied under the hypothesis of a homogeneous population in a region, then the epidemic is assumed to be particular to each duple <rg,ss> and the equations are formulated depending on <rg,ss>. The advantage of this approach will be visualized when the epidemic model is coupled with the management of health resources and control policies, which can be individualized for each duple <rg,ss>.

The model parameters can be grouped by the original source of variation, these sources are:

- Pathogen: characteristics of the epidemic due to the pathogen
- Age: It is typical for recovery/worsening times (rates) and probability of recovery to be a function of age.
- Economic stratum: influences the epidemic by means of the intensity of contact, product of the number of contacts, the duration of contacts and the closeness, these variables may also be a combined function of age and economic.

Additionally, may be considered people coming for the exogenous systems (out of the microregion) to the region.

The indexes used in the modeling are presented in the next table.

INDEXES		
Index HEA	**Short Description (Entities)**	**Long Description**
ag	Age	Age
mr	Macro-region	Macro-Region
rg, ro, rd	Region	Region (Basic Territory Unit)
ss	Social Segment	Socio-Demographic Segment
st, s1	Epidemic State	Epidemic State
t, q	Period	

In the Bogotá case, the socio-demographic segments are a combination of age with an economic stratum. The biological parameters depend on age.

2. GENERAL SIMULATION EPIDEMIC MODEL

Below is presented an aggregate model of epidemic that is the result of integrating the **SIR** model, **SEIR** and **SEI3RD**; in these standard models the population is grouped in only one homogenous group. **SEIMR/R-S** extends the modeling to a multi-segment-sociodemographic multi-region system.

SEIMR/R-S model describes the epidemic with following states:

S **Susceptible:** initially covers all population that potentially can be infected (SU)

E **Exposed:** Population that has been infected and are in an incubation (latency) period (EX). The model SIR does not include this state.

IM **Multi-Infected:** Population that has been infected and has active the pathogen in different states of development (I0, I1,I2, … , IN). The active infected states are ordered according to the severity of the infection. The modeled SIR and SEIR consider only one infected state. For convenience, the last state is called "IN"

R **Recovered:** Recovering population (RE)

R-S is related with the Region-Segment model that considers multiples regions where live people classified in multiples socio-demographics segments.

The next table shows the relation between models and epidemic states.

Model	SEIMR/R-S Model Epidemic States												
	Standard								Extended			Capacity	
	SU	EX	I_0	I_1	I_2	...	I_N	RE	NP	ED	ND	IU	CD
SIR	x						x	x					
SEIR	x	x					x	x					
SEI3RD	x	x	x	x	x	x	x	x		x			
SEIMR/R-S	x	x	x	x	x	x	x	x	x	x	x	x	x

The biological parameters used in the are described below (it includes the "standard" original formulation and the OPTEX formulation).

BIOLOGICAL PARAMETERS (READ)					
Parameter	**OPTEX Parameter**	**Table**	**Description**	**Measure Unit**	**Model**
PATHOGEN BIOLOGICAL PARAMETERS – SIR/SEIR					
δ	DELT	PBIO_GEN	Contact Intensity – Exogenous Parameter	peo-day	SIR
ω	PTRA	PBIO_GEN	Probability of transmission per contact intensity (infectivity)		
γ	GAGA	PBIO_GEN	Recovery rate for clinically ill (independent of age)	fpo/day	SIR
γ_{st}	GAGA	PBIO_GEN	Recovery rate for clinically ill (independent of age). It depends of st for SEIR3D	fpo/day	SIR
ζ	ZETA	PBIO_GEN	Epidemic death rate (independent of age)	fpo/day	SIR
μ^N	MIUN	PBIO_GEN	Natural mortality rate (independent of age)	fpo/day	
κ	KAPP	PBIO_GEN	The latency period of the virus before developing	day	SEIR
AGE BIOLOGICAL PARAMETERS – REGIONAL – SEGMENTED					
μ_{ag}	$MIUU_{ag}$		Epidemic mortality rate (complication rate, age dependent).	fpo/day	R-S
$\gamma\alpha_{ag}$	$GAMU_{ag}$		Recovery rate for clinically ill (age dependent)	fpo/day	R-S
EXOGENOUS SYSTEM PARAMETERS – SEIR					
λ_E	$LAME_{rg,ss}$	UBT_SDS	Exposed rate coming from the exogenous system	fpo/day	
λ_S	$LAMS_{rg,ss}$	UBT_SDS	Susceptible rate coming from the exogenous system	fpo/day	
λ_I	$LAMI_{rg,ss}$	UBT_SDS	Infectious rate coming from the exogenous system	fpo/day	
λ_R	$LAMR_{rg,ss}$	UBT_SDS	Recovered rate coming from the exogenous system	fpo/day	
BIOLOGICAL PARAMETERS – SEIR					
	$BEQU_{rg,ss}$		Parameter β for confinement control policies (SIR)		

The calculated biological parameters used are

BIOLOGICAL PARAMETERS (CALCULATED)					
Parameter	**Equation**	**OPTEX Parameter**	**OPTEX Equation**	**Description**	**Measure Unit**
ψ	$1/\kappa$	FHII	1/KAPP	Inverse virus latency period	1/day
β	$\delta\delta \times \omega$	BETA	DEI1 × PTRA	Inverse contact intensity × infectivity	1/fpo-day
	δ^{-1}	DEI1	1/DELT	Inverse contact intensity	
$\mu\upsilon_{ag}$	$\Sigma_{ag\in AGS(ss)}\ \mu_{ag}$	$MISS_{ss}$	$\Sigma_{ag\in AGS(ss)}\ MIUU_{ag}$		
$\gamma\gamma_{ag}$	$\Sigma_{ag\in AGS(ss)}\ \mu_{ag}$	$GASS_{ss}$	$\Sigma_{ag\in AGS(ss)}\ GAMU_{ag}$		
$\gamma\mu_{ss}$	$\Sigma_{ag\in AGS(ss)}\ (\gamma_{ag} + \mu_{ag})$	$GAZE_{ss}$	$GASS_{ss} + MISS_{ss}$		

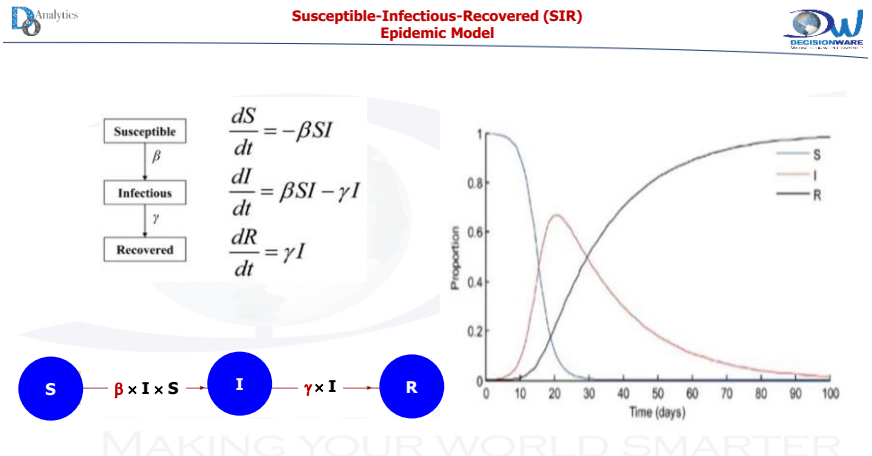
The calculus of parameters is analyzed in a posterior section, in the presentation of Bogotá case.

The general assumptions for standard epidemic models are:
- No vaccine exists
- The susceptible population is reduced through infection (moving to infective state).
- People who recovered after catch the virus will be insusceptible of it
- The population of infective class is increased by a fraction of susceptible individuals becoming infective.
- All other people are susceptible
- The population is homogenous
- The population of "critical" infective individuals is reduced by recovery from the disease.

2.1. SIR: EPIDEMIC MODEL

The **SIR** model is a basic model in epidemic modeling (Kermack and Mc Kendrick, 1927). **SIR** process, starting with a susceptible host who becomes infected, the class of infection grow for the infected individuals to be able to transmit the infection to susceptible. When the infected individual is no longer able to transmit infection to susceptible individual, the infected individual is removed from the cycle of diseases transmission in the population. This model is based on the following assumption:

Then, the basic **SIR** model describes the epidemic with three states:
S Susceptible: initially covers all population that potentially can be infected **(SU)**
I Infected: Population that has been infected (IN)
R Recovered: Recovering population (RE)
The diagram shows the behavior of **S(t)**, **I(t)**, and **R(t)** when they are normalized to total of population (**TPOB**) equal to 1.



The basic **SIR** model is represented based on three differential equations based on proportions of people in each state (the ratio between the people in a state with the initial population **TPOB**). The measurements in blue.

$$\partial \mathbf{S(t)}/\partial \mathbf{t}\ \text{(fpo/day)} = -\ \beta\ \text{(1/fpo-day)} \times \mathbf{I(t)}\ \text{(fpo)} \times \mathbf{S(t)}\ \text{(fpo)}$$

$$\partial \mathbf{I(t)}/\partial \mathbf{t}\ (\text{fpo/day}) = \beta\ (1/\text{fpo-day}) \times \mathbf{I(t)}\ (\text{fpo}) \times \mathbf{S(t)}\ (\text{fpo}) - \gamma\ (\text{fpo/day}) \times \mathbf{I(t)}\ (\text{fpo})$$

$$\partial \mathbf{R(t)}/\partial \mathbf{t}\ (\text{fpo/day}) = \gamma\ (\text{fpo/day}) \times \mathbf{I(t)}\ (\text{fpo})$$

where **S(t)**, **I(t)**, **R(t)** represent the population of susceptible, infected and recovered individuals, respectively. Adding these equations, the following condition must be hold

$$\partial \mathbf{S(t)}/\partial \mathbf{t} + \partial \mathbf{I(t)}/\partial \mathbf{t} + \partial \mathbf{R(t)}/\partial \mathbf{t} = \mathbf{0}$$

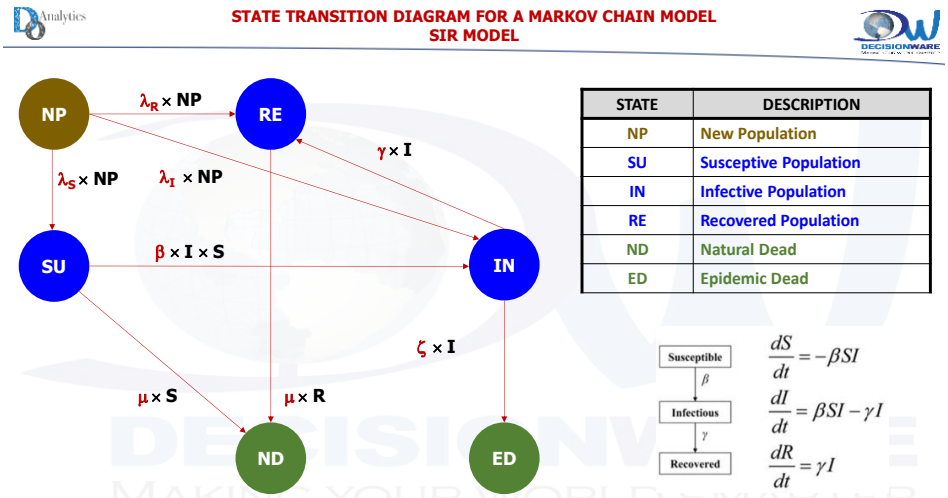
Additionally, **SIR** can be extended with other epidemic states for a more complete description of the system/epidemic:

NP New population entering the system, as people from abroad who in many cases are the ones who cause the epidemic (NP).

ED People who die due to the epidemic (these people die regardless of the management of the epidemic (D).

ND People who die from natural death (N)

ND and **ED** states should be included if it wants to account for the resources consumed by people who die, who are killed due the epidemic and due by causes other than the epidemic. The **NP(t)** state represent the proportion of people arriving from an exogenous system, may be births or people arriving from a foreign country/region. The value of **NP(t)** is a border condition with the foreign system over any value of **t** it is calculated taking as reference the initial population **TPOB**. This adjustment is made in all epidemic model included in the optimization model.



Then, the differential equations must be adjusted:

$$\partial S(t)/\partial t = -\beta \times I(t) \times S(t) + \lambda^S \times NP(t) - \mu^N \times S(t)$$

$$\partial I(t)/\partial t = \beta\ (I(t) \times S(t) - (\gamma + \zeta)\ ] \times I(t) + \lambda^I \times NP(t)$$

$$\partial R(t)/\partial t = \gamma \times I(t) - \mu^N \times R(t) + \lambda^R \times NP(t)$$

$$\partial D(t)/\partial t = \zeta \times I(t)$$

$$\partial N(t)/\partial t = \mu^N \times S(t) + \mu^N \times R(t)$$

where μ^N represents the natural mortality rate and λ^{st} the rates coming from the exogenous system to the state st.

If **TPOB** is the initial total population, and it is constant over time, **NP(t)=0**, the model meets the hypothesis that at all times

$$\mathbf{S(t) + I(t) + R(t) + D(t) + N(t) = 1}$$

If **NP(t)** is different from zero the previous equation must be adjusted as

$$\mathbf{S(t) + I(t) + R(t) + D(t) + N(t) = 1 + \int_{q\in[0,t]} \partial NP(q)\, \partial q}$$

To simulate the process the border conditions at the beginning of the simulation horizon are: **S(0), I(0), R(0), D(0)** and **NP(t),** for all **t.**

Assuming **NP(t)** equal to zero, the ratio $\rho = \gamma/\beta$ is called the relative removal rate. Thus, dynamics of infectious depends on the following ratio:

$$\mathbf{R_0 = S(0) \times \gamma/\beta}$$

where $\mathbf{R_0}$, called the basic reproduction ratio/number, is defined as the number of secondary infections produced by a single infectious individual during his/her entire infectious period. The role of the basic reproduction number is especially important. However, the following mathematical analysis describes how the basic reproduction number depends on the host population and the infected host.

At time **t = 0**, $\partial \mathbf{I}/\partial \mathbf{t}$ can be written as

$$\mathbf{\partial I/\partial t = (R_0 - 1) \times \gamma \times I(0)}$$

if $\mathbf{R_0} > 1$ then $\partial \mathbf{I}/\partial \mathbf{t} > 0$ and therefore the disease can spread; but if $\mathbf{R_0} < 1$ then the disease dies out. Making mathematical manipulation it is possible to prove that the maximum number of infective at any time is

$$\mathbf{TPOB\ (1 - \rho\ + \rho\ \ln [\ \rho\ /\ S(0)\ ]\ )}$$

It should be noted that the probability of transition becomes a dynamic variable that must be calculated by the mathematical model, for that reason the **t** index must be included.

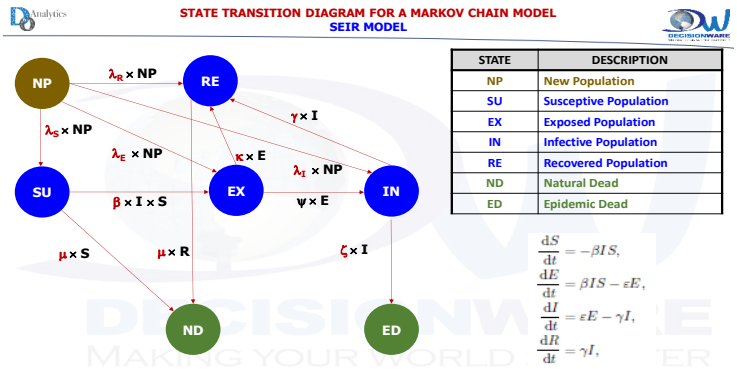
2.2. SEIR EPIDEMIC MODEL

There are multiple versions of the SEIR model, below are some images summarizing some of the literature consulted.

SOME SEIR MODELS	
Radulescu & Cavanagh (2020) $\frac{dS}{dt} = -\beta S(I+qE)/N$ $\frac{dE}{dt} = \beta S(I+qE)/N - \delta E$ $\frac{dI}{dt} = \delta E - \gamma I$ $\frac{dR}{dt} = \gamma I$	Hethcote, H. W. (2000). $\frac{dS}{dt} = -\beta\frac{IS}{N} - \mu S + rN + \delta R$ $\frac{dE}{dt} = \beta\frac{IS}{N} - (\mu+\sigma+\kappa)E$ $\frac{dI}{dt} = \sigma E - (\mu+\alpha+\gamma)I$ $\frac{dR}{dt} = \kappa E + \gamma I - \mu R - \delta R$ and $S + E + I + R = N$
Carcione et a. (2020)	Pang, W. (2020).

SOME SEIR MODELS	
$\dot{S} = \Lambda - \mu S - \beta S\frac{I}{N},$ $\dot{E} = \beta S\frac{I}{N} - (\mu + \epsilon)E,$ $\dot{I} = \epsilon E - (\gamma + \mu + \alpha)I,$ $\dot{R} = \gamma I - \mu R,$	$\frac{dS_t}{dt} = -\alpha^I S_t I_t - \alpha^E \beta^E S_t E_t$ $\frac{dE_t}{dt} = \alpha^I S_t I_t + \alpha^E \beta^E S_t E_t - \beta^I E_t - \mu^E \beta^E E_t$ $\frac{dI_t}{dt} = \beta^I E_t - \gamma I_t - \mu^I I_t$ $\frac{dR_t}{dt} = \gamma I_t$ $\frac{dD_t}{dt} = \mu^I I_t + \mu^E \beta^E E_t$
Liu and Liang (2013). $\begin{cases} \frac{dS}{dt} = -\beta < k > S(t)I(t) \\ \frac{dE}{dt} = \beta < k > S(t)I(t) - \beta < k > S(t-\tau)I(t-\tau) \\ \frac{dI}{dt} = \beta < k > S(t-\tau)I(t-\tau) - (d+\delta)\ I(t) \\ \frac{dR}{dt} = \delta I(t) \end{cases}$	Grimm et al. (2020) $\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta IS,$ $\frac{\mathrm{d}E}{\mathrm{d}t} = \beta IS - \varepsilon E,$ $\frac{\mathrm{d}I}{\mathrm{d}t} = \varepsilon E - \gamma I,$ $\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I,$

The classic SEIR model (Hethcote, 2000) describes the epidemic dynamics based on the transitions between four different compartments: susceptible (S), exposed (E), infectious (I), and recovered (R) individuals. The SEIR symbols are the same SIR symbols plus the parameter **ψ** that represents the inverse of the virus latency/incubation period (**κ**).



The equations of **SEIR** model are the same as those of **SIR** model considering the following changes:

- Equation **∂E(t)/∂t** is introduced

$$\partial E(t)/\partial t = \beta \times I(t) \times S(t) - \psi \times E(t) + \lambda^E \times NP(t)$$

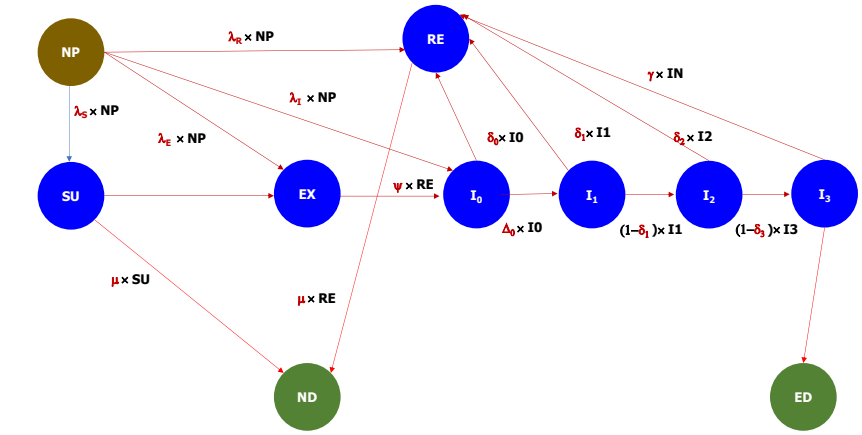
- Equation **∂I(t)/∂t** is modified

$$\partial I(t)/\partial t = \psi \times E(t) - (\gamma + \zeta) \times I(t) + \lambda^I \times NP(t)$$

2.3. SEI3RD EPIDEMIC MODEL

SEI3RD was developed with the aim of simulating the transmission and evolution of acute infections. This simulation assumes that the pathogen causes an infection followed by lifelong immunity or death through multiple infected states. **SEI3RD** model extended the classic SEIR model to distinguish between several categories of infectiousness; for example: asymptomatic, symptomatic, moderate, severe cases, and … . Being able to explicitly distinguish these different infected groups is important as they can greatly differ in terms of their underlying parameters as well as in terms of their behavioral response to public health interventions compared with the SEIR Model.

STATE TRANSITION DIAGRAM - SEI3RD EPIDEMIC MODEL



The transition between infected states follows this assumptions:

- A person can only be infected by one of the individuals belonging to one of the infected states (**I_0, I_1, I_2, I_3, … , I_N**).
- Being inoculated by the pathogen, the individual passes to the group of exposed E.
- After the latency period, the person in the exposed state becomes asymptomatic infectious (I_0 state).
- Once the person is in I_{st} state, there are two possible outcomes: worsening clinical status (moving to mild/moderate/critical infected I_{st+1}) or recovery (R).
- If the person recovers, in any of the states of infection, they enter the absorbent recupered state (R).
- Similar logic applies for a larger number of states of infection. It is understood that if an individual of the last state of infection (I3) worsens its clinical condition if it die (enters state E).

BIOLOGICAL PARAMETERS – SEIMR/R-S (READ)				
SEI3RD Parameter		**SEIMR/R-S Parameter**	**Description**	**Measure Unit**
$\delta_0, \delta_1, \delta_2, \delta_3$	δ_{st}	$DELX_{ag,st}$	Probability of I_0, I_1, I_2, I_3, … recovering without worsening the clinical condition. Depends of the epidemic state and the age.	
$\pi_0, \pi_1, \pi_2, \pi_3$	π_{st}	$PHIX_{ag,st}$	Time a patient in I_0, I_1, I_2, I_3, … recovers	day
$\eta_0, \eta_1, \eta_2, \eta_3$	η_{st}	$ETAX_{ag,st}$	Time a patient in I_0, I_1, I_2, I_3, … to next infected state (develops symptoms, requires hospitalization, requires UCI, dies)	day

BIOLOGICAL PARAMETERS (CALCULATED)					
Para meter	**Equation**	**SEIMR/R-S Parameter**	**SEIMR/R-S Equation**	**Description**	**Measure Unit**
γ_{st}	$1/\pi_{st}$	$GAMX_{ag,st}$	$1/PHIX_{ag,st}$	Fraction of people in I_0, I_1, I_2, I_3, … who recover in one day	fpo/day
σ_{st}	$1/\eta_{st}$	$RHOX_{rg,ss}$	$1/ETAX_{ag,st}$	Fraction of people in I_0, I_1, I_2, I_3, … who complicate in one day	fpo/day
ψ	$1/\kappa$	FHII	1/KAPP	Inverse virus latency period	1/day
AUXILIARY PARAMETERS					
$\delta\gamma_{st}$	$\delta_{st}\ \gamma_{st}$	$DEGX_{ag,st}$	$DELX_{ag,st} \times GAMX_{ag,st}$	$\delta\gamma_{st} = \delta_{st}\ \gamma_{st}$	
$\sigma\delta_{st}$	$\delta_{st}\ \sigma_{st}$	$RODX_{ag,st}$	$DELX_{ag,st} \times RHOX_{rg,ss}$	$\delta\sigma_{st} = (1-\delta_{st})\ \sigma_{st} = \sigma_{st} - \delta_{st}\ \sigma_{st}$	
$\delta\sigma_{st}$	$(1-\delta_{st})\ \sigma_{st}$	$DERX_{ag,st}$	$RHOX_{rg,ss} - RODX_{ag,st}$	$\delta\sigma_{st} = (1-\delta_{st})\ \sigma_{st} = \sigma_{st} - \delta_{st}\ \sigma_{st} = \sigma_{st} - \sigma\delta_{st}$	
$\delta\delta_{st}$	$\delta_{st}\ \gamma_{st} + (1-\delta_{st})\ \sigma_{st}$	$DGRX_{ag,st}$	$DEGX_{ag,st} + DERX_{ag,st}$	$\delta\delta_{st} = (\delta_{st}\ \gamma_{st} + (1-\delta_{st})\ \sigma_{st}) = \delta\gamma_{st}$	

The equations of **SEI3RD** model are the same as those of **SEIR** model considering the following changes:

- Equations **$\partial S(t)/\partial t$** is modified

$$\partial S(t)/\partial t = -\beta \times [\ \Sigma_{st \in INF}\ I_{st}(t)\ ] \times S(t) + \lambda^S \times NP(t) - \mu^N \times S(t)$$

- Equations **$\partial E(t)/\partial t$** is modified

$$\partial E(t)/\partial t = \beta \times [\ \Sigma_{st\in INF}\ I_{st}(t)\ ] \times S(t) - \psi \times E(t) + \lambda^{E} \times NP(t)$$

- Equation **$\partial I(t)/\partial t$** is substituted by the equations **$\partial I_0(t)/\partial t$**

$$\partial I_0(t)/\partial t = \psi \times E(t) - \delta\delta_0 \times I_0(t) + \lambda^{I} \times NP(t)$$

$$\delta\delta_{st} = (\delta_{st} \times \gamma_{st} + (1-\delta_{st}) \times \sigma_{st})$$

- Equation **$\partial I(t)/\partial t$** is substituted by the equations **$\partial I_{st}(t)/\partial t$**

$$\partial I_{st}(t)/\partial t = \delta\sigma_{st-1} \times I_{st-1}(t) - \delta\delta_{st} \times I_{st}(t)$$

$$\delta\sigma_{st} = (1 - \delta_{st}) \times \sigma_{st}$$

- Equations **$\partial R(t)/\partial t$** is modified

$$\partial R(t)/\partial t = \Sigma_{st\in INF}\ \delta\gamma_{st} \times I_{st}(t) - \mu^{N} \times R(t) + \lambda^{R} \times NP(t)$$

$$\delta\gamma_{st} = \delta_{st} \times \gamma_{st}$$

- Equations **$\partial D(t)/\partial t$** is modified

$$\partial D(t)/\partial t = \Sigma_{st\in IF}\ \zeta \times I_{st}(t)$$

$$\zeta = \delta\sigma_{N} = (1 - \delta_{N})\ \sigma_{N}$$

These equations are the equations of the SEIMR model

3. SEIMR/R-S GENERAL EPIDEMIC MODEL

The equations of the SEIMR model are presented in the next table.

	SEIMR - Differential Equations				
State	st∈SET	State Increment	State Decrement	Natural Dead	Exogenous Increment
$\partial S(t)/\partial t$	SU	$+\lambda^{S} \times NP(t)$	$\beta \times IS(t) \times S(t)$	$\mu^{N} \times S(t)$	$\lambda^{S} \times NP(t)$
$\partial E(t)/\partial t$	EX	$\beta \times IS(t) \times S(t)$	$\psi \times E(t)$		$\lambda^{E} \times NP(t)$
$\partial I(t)/\partial t$	IN	$\beta \times IS(t) \times S(t)$	$\delta\delta_{st} \times I_{st}(t)$		$\lambda^{I} \times NP(t)$
$\partial I_0(t)/\partial t$	I0	$\psi \times E(t)$			$\lambda^{I} \times NP(t)$
$\partial I_{st}(t)/\partial t$	I1F	$\delta\sigma_{st-1} \times I_{st-1}(t)$			
$\partial R(t)/\partial t$	RE	$\Sigma_{st\in I1F}\ \delta\gamma_{st} \times I_{st}(t)$		$\mu^{N} \times R(t)$	$\lambda^{R} \times NP(t)$
$\partial D(t)/\partial t$	ED	$\Sigma_{st\in IF}\ \zeta \times I_{st}(t)$			
		AUXILIARY EQUATION			
		$IS(t) = [\ \Sigma_{st\in INF}\ I_{st}(t)\ ]$			

These equations serve to represent any of the three models studied. The conditions are as follows:

1. SIR Model:
   - Only consider one infected state IN the definitions of the infected state sets are: st∈IF={IN}, st∈I1F={}, st∈I0={}, st∈INF={IN} and st∈IN={IN}
   - Do not include the exposed state (E), that means that st∈EX={}

2. SEIR Model
   - Only consider one infected state IN the definitions of the infected state sets are equal to SIR model.

3. SEIMR Model

- Considered multiples infected stats {I0, I1, I2,… , IN} IN associate to I_N, do not include the state I_0 that means:
  st∈IF={I_N}, st∈I1F={I_1, I_2, … , I_N}, st∈I0={I_0}, st∈INF={I_0, I_1, I_2, … , I_N} and st∈IN={}

The next table presents the SETs of epidemic states needed to model the three epidemics models. The infected sets permit to model any of the three models with the same equations; they are used to define the existence conditions of the equations and in summation limits into the equations.

Epidemic States SETs											
Model	Epidemic States	Non Infected States					Infected States				
	STA	SU	EX	RE	ED	ND	INF	IN	I0	I1F	IF
SIR	S, I, R, D, N	S		R	D	N	I	I			
SEIR	S, E, I, R, D, N	S	E	R	D	N	I	I			
SEIMR	S, E, I_0, I_1, I_2, … , I_N, D, N	S	E	R	D	N	I_0, I_1, I_2, … , I_N		I_0	I_1, I_2, … I_{N-1}	I_N

3.1. GENERAL FRAMEWORK

To formulate the regional model segmented socio-demographically the following hypotheses are assumed:

3.1.1. REGIONAL MODELING

- There is no contagion between people living in different regions. This can be true for large regions such as states or departments. But it is questionable for metropolitan areas (cities and conurbed regions) where there is intense traffic between regions.

- The inter-region interrelationship is modeled on the following assumptions:
  - There is traffic of people between regions, which sets for each pair of regions the fraction of each segment, $\varphi_{ro,rg,ss}$, moving from the source region (ro) to the destination region (rg).
  - In addition, the fraction of the time, $\phi_{ro,rg,ss}$, is known to people from the region origin in the destination region during the period (one day).

The calculation process involves determining the impact on the spread of the virus that the population movement has for this purpose it is calculated using the number of infected people who can move between two regions multiplied by the fraction of the time spent in the destination locality. This implies the following effects on the diffusion rate:

1. Infected Movements

- Increasing the rate of diffusion in the destination locality due to those infected by coming from other regions, it is calculated as:

$$\mathbf{II_{rg}(t) = \Sigma_{ss\in SSR(rg)} \Sigma_{ro\in ROR(rg)} \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times IS_{ro,ss}(t)}$$

- Decreased diffusion rate in the source region due to the infected by moving to other regions, it is calculated as:

$$\mathbf{IE_{rg}(t) = \Sigma_{ss\in SSR(rg)} \Sigma_{rd\in RDE(rg)} \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times IS_{rg,ss}(t)}$$

The net effect on the rg-region will be:

$$\mathbf{IS_{rg,ss}(t) = \Sigma_{st\in INF} I_{st,rg,ss}(t)}$$

$$\mathbf{IX_{rg}(t) = \Sigma_{ss\in SSR(rg)} IS_{rg,ss}(t)}$$

$$\mathbf{IR_{rg}(t) = IX_{rg}(t) + II_{rg}(t) - IE_{rg}(t)}$$

where

$I_{st,rg,ss}(t)$ fraction of the population infected in st-epidemic-state living in rg-region and ss-segment.
$IS_{rg,ss}(t)$ fraction of the population infected living in rg-region and ss-segment.
$IX_{rg}(t)$ fraction of the population infected living in rg-region
$II_{rg}(t)$ weighted fraction of the population infected traveling to rg-region
$IE_{rg}(t)$ weighted fraction of the population infected traveling from rg-region

2. Susceptible Movements

- Increasing the rate of diffusion in the destination locality (rg-region) due to those susceptible people by coming from other regions that may be infected in rg-region, it is calculated as:

$$SI_{ro,rg,ss}(t) = \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times S_{ro,ss}(t)$$

- Decreased diffusion rate in the source region (rg-region) due to the susceptible people by moving to other regions that cannot be infected in rg-region, it is calculated as:

$$SE_{rg,rd,ss}(t) = \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times S_{rd,ss}(t)$$

The susceptible population living in the rg-region ss-segment must be decremented by the susceptible people belonging to other regions:

$$SN_{rg,ss}(t) = S_{rg,ss}(t) - \Sigma_{rd \in RDE(rg)} SE_{rg,rd,ss}(t)$$

where

$S_{rg,ss}(t)$ fraction of the susceptible population living in rg-region and ss-segment.
$SI_{ro,rg,ss}(t)$ fraction of the ss-segment susceptible population traveling from ro-region to rg-region
$SE_{rg,rd,ss}(t)$ fraction of the ss-segment susceptible population traveling from rg-region to rd-region

3.1.2. SOCIO DEMOGRAPHIC SEGMENT MODELING

- An infected person in any segment can infect anyone susceptible in any socio-demographic segment.

The calculation process implies that at the level of one region the population of any segment can infect the population of any other segment. To do this, diffusion (infection of susceptible from infected) is managed at a detailed level in the differential equations for all infected states, but in the differential equation the infected transmission is calculated based on the summation of all infected states in all ss-segments.

The contagion of the susceptible population living in the rg-region and belonging to the ss-segment will be the sum of the contagions that occur in the rg-region (people that do not travel out of the rg-region) plus the contagions that occur in the rd-regions (destination regions) this is

$$S2I_{rg,ss}(t) = \beta \times (IR_{rg}(t) \times SN_{rg,ss}(t) + \Sigma_{rd \in RDE(rg)} IR_{rd}(t) \times SE_{rg,rd,ss}(t))$$

3.2. GENERAL FRAMEWORK

The differential equations of the regional-segmented model are:

$$\partial S_{rg,ss}(t)/\partial t = - S2I_{rg,ss}(t) - \mu^{N} \times S_{rg,ss}(t) + \lambda^{S}_{rg,ss} \times NP(t)$$

$$\partial E_{rg,ss}(t)/\partial t = S2I_{rg,ss}(t) - \psi \times E_{rg,ss}(t) + \lambda^{E}_{rg,ss} \times NP(t)$$

st∈IN

$$\partial I_{st,rg,ss}(t)/\partial t = S2I_{rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I0

$$\partial I_{st,rg,ss}(t)/\partial t = S2I_{rg,ss} - \gamma\sigma_{st,ss} \times I_{rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I1F

$$\partial I_{st,rg,ss}(t)/\partial t = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\sigma_{st,ss} \times I_{st,rg,ss}(t)$$

st∈IF

$$\partial I_{st,rg,ss}(t)/\partial t = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t)$$

$$\partial R_{rg,ss}(t)/\partial t = \Sigma_{st\in I1F}\, \gamma\sigma_{st-1,ss} \times I_{st,rg,ss}(t) - \mu^{N} \times R_{rg,ss}(t) + \Sigma_{ss\in SSR(rg)}\, \lambda^{R}_{rg,ss} \times NP(t)$$

$$\partial D_{rg,ss}(t)/\partial t = \Sigma_{st\in I1F}\, \mu\sigma_{ss} \times I_{st,rg,ss}(t)$$

$$\partial NR_{rg}(t)/\partial t = \mu^{N} \times SR_{rg,ss}(t) + \mu^{N} \times RR_{rg}(t)$$

Where $\gamma\zeta_{st,ss}$, $\mu\sigma_{ss}$ and $\gamma\sigma_{st,ss}$ are rates (parameters) that depends on the configuration of the socio-demographics segments. In this case they are defined as

$$\gamma\zeta_{st,ss} = \Sigma_{ag\in AGS(ss)}\, (\gamma\alpha_{st,ag} + \mu_{ag})$$
$$\mu\sigma_{ss} = \Sigma_{ag\in AGS(ss)}\, \mu_{ag}$$
$$\gamma\sigma_{st,ss} = \Sigma_{ag\in AGS(ss)}\, \gamma\alpha_{st,ag}$$

The definition equations of the regional-segmented model are:

$$IS_{rg,ss}(t) = \Sigma_{st\in INF}\, I_{st,rg,ss}(t)$$
$$IX_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, IS_{rg,ss}(t)$$
$$II_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, \Sigma_{ro\in ROR(rg)}\, \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times IS_{ro,ss}(t)$$
$$IE_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, \Sigma_{rd\in RDE(rg)}\, \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times IS_{rg,ss}(t)$$
$$IR_{rg}(t) = IX_{rg}(t) + II_{rg}(t) - IE_{rg}(t)$$

$$SR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, S_{rg,ss}(t)$$
$$SI_{ro,rg,ss}(t) = \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times S_{ro,ss}(t)$$
$$SE_{rg,rd,ss}(t) = \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times S_{rd,ss}(t)$$
$$SN_{rg,ss}(t) = S_{rg,ss}(t) - \Sigma_{rd\in RDE(rg)}\, SE_{rg,rd,ss}(t)$$
$$SIN_{rg}(t) = IR_{rg}(t) \times SN_{rg,ss}(t)$$
$$SIE_{rg}(t) = \Sigma_{rd\in RDE(rg)}\, IR_{rd}(t) \times SE_{rg,rd,ss}(t)$$
$$S2I_{rg,ss}(t) = \beta \times SIN_{rg}(t) + \beta \times SIE_{rg}(t)$$

$$RR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, R_{rg,ss}(t)$$

$$DR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\, D_{rg,ss}(t)$$

From now on, the above mathematical definitions will be summarized as

$$\mathbf{\{\, S, E, I_{st}, D, N \,\} \in \Theta}$$

The next table shows the equations dividing the increment and the decrement on each state, it must be considered in the implementation of the mathematical models. The table includes the sets that defined the existence of the equations manly for the infected states.

	SIR Regional – Segmented Model - Differential Equations				
Set	State	State Increment	State Decrement	Natural Dead	Exogenous Increment
	REGIONAL - SEGMENT EQUATIONS				
SU	$\partial S_{rg,ss}(t)/\partial t$		$S2I_{rg,ss}(t)$	$\mu^{N} \times S_{rg,ss}(t)$	$\lambda^{S}_{rg,ss} \times NP(t)$
EX	$\partial E_{rg,ss}(t)/\partial t$	$S2I_{rg,ss}(t)$	$\psi \times E_{rg,ss}(t)$		$\lambda^{E}_{rg,ss} \times NP(t)$
I0	$\partial I_{st,rg,ss}(t)/\partial t$	$\psi \times E_{rg,ss}(t)$	$\gamma\zeta_{st,ss} \times I_{st,rg,ss}(t)$		$\lambda^{I}_{rg,ss} \times NP(t)$

	SIR Regional – Segmented Model - Differential Equations				
Set	State	State Increment	State Decrement	Natural Dead	Exogenous Increment
I1F		$\gamma\zeta_{st-1,ss} \times I_{st-1,rg,ss}(t)$			
IF			$\gamma\sigma_{st,ss} \times I_{st,rg,ss}(t)$		
IN		$- S2I_{rg,ss}(t)$			$\lambda^{I}_{rg,ss} \times NP(t)$
RE	$\partial R_{rg,ss}(t)/\partial t$	$\Sigma_{st\in I1F}\ \gamma\sigma_{st,ss} \times I_{st,rg,ss}(t)$		$\mu^{N} \times R_{rg,ss}(t)$	$\lambda^{R}_{rg,ss} \times NP(t)$
ED	$\partial D_{rg,ss}(t)/\partial t$	$\mu\sigma_{ss} \times I_{rg,ss}(t)$			
ND	$\partial NR_{rg}(t)/\partial t$	$\mu^{N} \times (SR_{rg}(t) + RR_{rg}(t))$			

SUSCEPTIBLE STATES EQUATIONS
$SR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ S_{rg,ss}(t)$
$SI_{ro,rg,ss}(t) = \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times S_{ro,ss}(t)$
$SE_{rg,rd,ss}(t) = \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times S_{rd,ss}(t)$
$SN_{rg,ss}(t) = S_{rg,ss}(t) - \Sigma_{rd\in RDE(rg)}\ SE_{rg,rd,ss}(t)$
$SIN_{rg}(t) = IR_{rg}(t) \times SN_{rg,ss}(t)$
$SIE_{rg}(t) = \Sigma_{rd\in RDE(rg)}\ IR_{rd}(t) \times SE_{rg,rd,ss}(t)$
$S2I_{rg,ss}(t) = \beta \times SIN_{rg}(t) + \beta \times SIE_{rg}(t)$
INFECTED STATES EQUATIONS
$IS_{rg,ss}(t) = \Sigma_{st\in INF}\ I_{st,rg,ss}(t)$
$IX_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ IS_{rg,ss}(t)$
$II_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ \Sigma_{ro\in ROR(rg)}\ \varphi_{ro,rg,ss} \times \phi_{ro,rg,ss} \times IS_{ro,ss}(t)$
$IE_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ \Sigma_{rd\in RDE(rg)}\ \varphi_{rg,rd,ss} \times \phi_{rg,rd,ss} \times IS_{rg,ss}(t)$
OTHER EPIDEMIC STATES EQUATIONS
$RR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ R_{rg,ss}(t)$
$DR_{rg}(t) = \Sigma_{ss\in SSR(rg)}\ D_{rg,ss}(t)$

3.3. DISCRETE EPIDEMIC MODEL

The differential equations must be redefined in algebraic terms (discrete equations). The discrete equivalent equations of differential equations are

$$[S_{rg,ss}(t+\Delta t) - S_{rg,ss}(t)]/\Delta t = - S2I_{rg,ss}(t) - \mu^{N} \times S_{rg,ss}(t) + \lambda^{S}_{rg,ss} \times NP(t)$$

$$[E_{rg,ss}(t+\Delta t) - E_{rg,ss}(t)]/\Delta t = S2I_{rg,ss}(t) - \psi \times E_{rg,ss}(t) + \lambda^{E}_{rg,ss} \times NP(t)$$

st∈IN

$$[I_{st,rg,ss}(t+\Delta t) - I_{st,rg,ss}(t)]/\Delta t = S2I_{rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I0

$$[I_{st,rg,ss}(t+\Delta t) - I_{st,rg,ss}(t)]/\Delta t = \beta \times IR_{rg,ss}(t) \times S_{rg,ss}(t) - \gamma\sigma_{st,ss} \times I_{rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I1F

$$[I_{st,rg,ss}(t+\Delta t) - I_{st,rg,ss}(t)]/\Delta t = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\sigma_{st,ss} \times I_{st,rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈IF

$$[I_{st,rg,ss}(t+\Delta t) - I_{st,rg,ss}(t)]/\Delta t = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t)$$

$$[R_{rg,ss}(t+\Delta t) - R_{rg,ss}(t)]/\Delta t = \Sigma_{st\in I1F}\ \gamma\sigma_{st-1,ss} \times I_{st,rg,ss}(t) - \mu^{N} \times R_{rg,ss}(t) + \Sigma_{ss\in SSR(rg)}\ \lambda^{R}_{rg,ss} \times NP(t)$$

$$[D_{rg,ss}\ (t+\Delta t) - D_{rg,ss}(t)]/\Delta t = \Sigma_{st\in I1F}\ \mu_{st,ag=AGS(ss)} \times I_{st,rg,ss}(t)$$

$$[NR_{rg}(t+\Delta t) - NR_{rg,ss}(t)]/\Delta t = \mu^{N} \times SR_{rg,ss}(t) + \mu^{N} \times RR_{rg}(t)$$

If **$\Delta t = 1$** (one day), the above equations correspond directly to those that must be included in the optimization model using mathematical programming.

$$S_{rg,ss}(t+1) - S_{rg,ss}(t) = - S2I_{rg,ss}(t) - \mu^{N} \times S_{rg,ss}(t) + \lambda^{S}_{rg,ss} \times NP(t)$$

$$E_{rg,ss}(t+1) - E_{rg,ss}(t) = S2I_{rg,ss}(t) - \psi \times E_{rg,ss}(t) + \lambda^{E}_{rg,ss} \times NP(t)$$

st∈IN

$$I_{st,rg,ss}(t+1) - I_{st,rg,ss}(t) = - S2I_{rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I0

$$I_{st,rg,ss}(t+1) - I_{st,rg,ss}(t) = \beta \times IR_{rg,ss}(t) \times S_{rg,ss}(t) - \gamma\sigma_{st,ss} \times I_{rg,ss}(t) + \lambda^{I}_{rg,ss} \times NP(t)$$

st∈I1F

$$I_{st,rg,ss}(t+1) - I_{st,rg,ss}(t) = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\sigma_{st,ss} \times I_{st,rg,ss}(t)$$

st∈IF

$$I_{st,rg,ss}(t+1) - I_{st,rg,ss}(t) = \gamma\sigma_{st-1,ss} \times I_{st-1,rg,ss}(t) - \gamma\zeta_{st,ss} \times I_{st,rg,ss}(t)$$

$$R_{rg,ss}(t+1) - R_{rg,ss}(t) = \Sigma_{st\in I1F}\, \gamma\alpha_{st,ag=AGS(ss)} \times I_{st,rg,ss}(t) - \mu^{N} \times R_{rg,ss}(t) + \Sigma_{ss\in SSR(rg)}\, \lambda^{R}_{rg,ss} \times NP(t)$$

$$D_{rg,ss}(t+1) - D_{rg,ss}(t) = \Sigma_{st\in I1F}\, \mu_{st,ag=AGS(ss)} \times I_{st,rg,ss}(t)$$

$$NR_{rg}(t+1) - NR_{rg,ss}(t) = \mu^{N} \times SR_{rg,ss}(t) + \mu^{N} \times RR_{rg}(t)$$

In addition, the definition restrictions should be considered

$$\mathbf{\{\, S, E, I_{st}, D, N \,\}} \in \Theta$$

4. CONTROLLED EXPERIMENTS

5. FUNDING

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